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# Enrolling Decisionally Impaired Adults in Clinical Research

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**Progress in diagnosing, treating, and preventing medical conditions that impair decision-making abilities depends on clinical research involving individuals who may be either unable to or have diminished ability to give informed consent. Such research, however, raises ethical concern and controversy about the potential exploitation of these vulnerable individuals. This article addresses a range of ethical and practical issues concerning the enrollment of adults who are decisionally impaired, and those at risk of becoming so, in clinical research. These include (1) the relationship of decision-making capacity to competence, and the framework for determining competence in adults receiving clinical care and making treatment decisions for those who lack competence; (2) the differences between clinical practice and clinical research that influence the criteria for permissible research involving incompetent adults and the applicability of the framework guiding treatment decisions to clinical research decisions; and (3) the regulatory framework developed to guide the ethical participation of children in research and its applicability to determining the scope and limits of research with incompetent adults.**

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The moral and legal acceptability of informed consent for research participation requires the voluntary and informed consent of a competent individual. Individuals with diminished ability to make rational decisions may not be competent to give informed consent for research participation. Nevertheless, evidence-based improvements in health care services and prevention efforts for a variety of medical conditions depend on research involving individuals with, or at risk for, decisional impairment. Yet enrolling decisionally impaired individuals in research is fraught with ethical peril as it challenges a fundamental norm of research ethics: that participants in research must give informed consent. How can needed progress be achieved without exploiting individuals who are unable to make informed choices to enroll in or withdraw from research?

Diminished decision-making ability is found in many common medical conditions. For example, the potential for compromised decision making is well recognized in neuropsychiatric disorders,[1] such as Alzheimer disease[2,3] and schizophrenia.[4] Significant contributors to the global burden of disease in the United States are also associated with cognitive impairment:[5] ischemic heart disease,[6] motor vehicle accidents,[7,8] cancer,[9] HIV/AIDS,[10] alcohol abuse and

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dependence,[11,12] cerebrovascular disease,[13] chronic obstructive pulmonary disease,[14,15] self-inflicted harms,[16] depression,[17] and diabetes.[18,19] Individuals with decisional impairment are treated in a variety of general medical treatment settings, including emergency departments,[6] intensive care units,[20,21] hospice and palliative care settings,[22,23] as well as in settings specialized for the care of patients with neuropsychiatric disorders, including nursing homes[24] and psychiatry and neurology units. Outcomes research aimed at improving treatment and prevention efforts for these conditions in real-world settings requires consideration of the issues raised by enrolling in research individuals with, or at risk for, decisional impairment.

This article addresses a range of ethical and practical issues concerning the enrollment of incompetent adults, and those at risk of becoming so, in clinical research. First we address the relationship between decision-making capacity and competence and discuss the framework for determining competence in adults receiving clinical care and making treatment decisions for those who lack competence. Then we address the differences between clinical practice and clinical research that influence the criteria for permissible research involving incompetent adults and the applicability of the framework guiding treatment decisions to clinical research decisions. We also discuss the regulatory framework developed to guide the ethical participation of children in research and its applicability to determining the scope and limits of research with incompetent adults.

## The Relationship Between Decision-Making Capacity and Competence

Adults are presumed competent to make their own decisions. The authority to deem an adult to be incompetent is vested in the judicial system, and rulings of incompetence are generally made in relation to a specific functional task (eg, write a will, manage ones own finances, make medical decisions). Review of judicial decisions regarding incompetence across a variety of tasks finds a common set of decision-making abilities to be important.[25] The evidence upon which judicial determination of competence relies includes a formal assessment of decision-making abilities by medical professionals with appropriate expertise. The clinical assessment is generally referred to as the assessment of decision-making capacity.

In the medical setting, practical constraints frequently preclude judicial review of an individual's competence. Expertise is readily available for performing capacity assessments, and it would be difficult to provide judicial review whenever a patient's competence is questioned. In this setting, informal judgments about competence based on these capacity assessments are generally accepted as reasonable proxies for judicial review. Consequently, the terms competence and capacity are often used interchangeably in the medical setting.

Nevertheless, competence and capacity are not the same. "Competence" refers to the legal and moral status of individuals that entitles them to make their own decisions. "Capacity" refers to the different cognitive, affective, and volitional abilities that underlie competence. Profound impairment of these abilities renders individuals incompetent and requires that others make decisions on their behalf. Judgments of competence function normatively to designate a dichotomous status (ie, permitted, or not permitted, to make decisions), whereas decision-making capacity varies along a spectrum from fully capacitated to totally incapacitated.[26] Individuals may be competent even though they suffer from diminished capacity. The threshold for incompetence varies depending upon the task an individual is called to perform. Unfortunately, limited empirical data are available to help determine appropriate thresholds. Therefore, the determination is generally made on a case-by-case basis. In this article, we use the terms "capacity" and "diminished capacity" to refer to results from the clinical assessment and "competence" and "incompetence" to refer to the judgment made about the status of individuals to make morally binding decisions for themselves.

### Framework for Determining Competence in the Treatment Context and Making Treatment Decisions for Incompetent Adults

Several important points of consensus have emerged for determining competence in the treatment context and making treatment decisions for incompetent adults.[26,27] First, competence is understood as relative to the type and complexity of the treatment decision at stake. Some decisionally

impaired patients are competent to make simple treatment decisions but are incompetent to make complex ones that require weighing and balancing the risks and benefits of alternative treatments and factoring in uncertainty about outcomes. The assessment of capacity that informs decisions about competence includes assessing the abilities: (1) to make and express a choice, (2) to understand information relevant to the treatment decision, (3) to appreciate the significance of this information to the individual's own situation, and (4) to reason with the relevant information in weighing options.[28] Neither mental status examinations nor medical diagnostic categories in themselves yield sufficient indicators of capacity or incapacity to make treatment decisions.[2] However, poor performance on mental status examinations suggests the need for a more formal capacity assessment. With the exception of conditions associated with loss of consciousness, lack of decision-making capacity cannot be reliably inferred solely from diagnostic categories. For example, although Alzheimer disease is associated with profound cognitive impairment, individuals in the early stages of this disorder are often still capable of making their own treatment decisions.

Second, thresholds for competence to make treatment decisions should adopt a "sliding scale."[29] Just as thresholds for competence vary according to the complexity and uncertainty embedded in the decision, the threshold should become more demanding as the risks of a treatment intervention and the uncertainty of its benefits increase.

Third, assessing capacity is the responsibility of the treating physician. In cases where competence is called into question, a psychiatric or neurologic consultation to more formally assess decision-making capacity may be indicated.

Fourth, when patients are judged incompetent to make treatment decisions, surrogate decision makers must be engaged. Two legal and ethical standards govern surrogate decision-making.[30] If the prior preferences of the patient are known, then the surrogate should make a "substituted judgment" that he or she believes the patient would have made if able; if not known, then the surrogate and physician choose the option believed to promote the patient's "best interests." Exceptions include emergency interventions or when surrogate decision makers cannot be found, in which case physicians make treatment decisions for the patient. Patients may designate surrogate decision makers through a durable power of attorney (DPA). Additionally, written guidance about the patient's treatment preferences may be available in the form of an advance directive or living will. The majority of patients have not engaged in such formal advance planning, although many may have informally communicated their preferences. If no surrogate has been designated in advance, next-of-kin are generally considered appropriate surrogate decision makers. It is presumed that they know best the preferences and values of the patient which should determine or inform treatment decisions and that they will be concerned to promote the patient's best interest.

## Differences Between Clinical Practice and Clinical Research

While the conceptual and ethical framework of decision-making about clinical care is largely applicable to the research context, it must be evaluated in light of ethically significant differences between clinical practice and clinical research. Individuals may receive treatment in both contexts, but the orientation of clinicians is markedly different. Ethically, clinical medicine is oriented toward "personal care."[31] Patients receive individualized care by physicians dedicated to the patient's best medical interests. The risks of diagnostic procedures and treatment interventions are justified solely by anticipated medical benefits to the patient.

Some aspects of personal care may operate in clinical research; however, as scientists, physician-investigators are interested in patients primarily as members of groups from which data can be obtained for answering scientific questions. Clinical research often imposes discomforts or risks of harm on patient-volunteers that are not compensated by personal medical benefits; these are justified, in the language of the US research regulations, by "the importance of the knowledge that may reasonably be expected to result."[32] For example, in clinical trials patient-volunteers may be randomized to treatment alternatives (or placebo), patient-volunteers and physician-investigators may be blind to which alternative is received, and protocol-driven limitations may be placed on the types and dosages of treatments. These features depart significantly from personal care. Clinical research can also include research procedures that

offer no direct diagnostic or therapeutic benefit for patient-volunteers.

## Criteria for Permissible Research With Incompetent Adults

Differences between clinical practice and clinical research affect the applicability of the framework developed for clinical care of incompetent adults to the research setting. Four specific issues deserve attention: (1) competence must include the ability to appreciate the differences between clinical practice and clinical research, (2) levels of risk that are justified in clinical practice may not be justifiable in clinical research, (3) a formal plan for capacity assessment may be necessary in some research protocols, and (4) surrogate decision making should take into account the differences between clinical practice and clinical research.

### Competence Must Include the Ability to Appreciate the Differences Between Clinical Practice and Clinical Research

While the same four types of abilities that constitute capacity to consent to treatment are relevant to capacity to consent to research,[33] capacity assessment in research is complicated because patient-volunteers may have a "therapeutic misconception," in which they perceive various research interventions as being intended primarily for their own individualized direct diagnostic or therapeutic benefit.[34,35] No agreement exists on how realistic it is to expect sick patients deciding to enroll in clinical research to be able to fully appreciate the differences between personal care and research participation. Nonetheless, the ability to appreciate these differences may be so impaired that some individuals, who may be capable of making treatment decisions, should be judged incapable of making research decisions.

To respect self-determination, the process of assessing capacity may need to be accompanied by interventions aimed at enhancing capacity. Persons who at a given time are judged to be incompetent to give informed consent for research may be brought to an adequate level of capacity in response to medical treatment or intensive educational efforts.[4,36]

If adults are incompetent to make decisions, they need protection to respect their rights and promote their best interests. The Belmont Report, a landmark report written in 1979 by a Presidential advisory committee, articulated ethical principles and guidelines for research involving human subjects, upon which many of the US federal regulations governing human subjects research were subsequently based.[32,37] It asserts that "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection."

Standards for enrolling incompetent individuals in clinical research require striking a balance between these two components of respect for persons. Incompetent persons should be protected either by excluding them from research participation to prevent their exploitation or by enrolling them in research subject to ethical safeguards. These include suitable limitations on permissible research in view of its purpose and anticipated risk-benefit profile and surrogate authorization and oversight.[37–39]

In general, enrolling incompetent individuals in research when not scientifically necessary is exploitative.[40] If valuable scientific studies can be conducted with subjects competent to give informed consent, then incompetent persons should not be enrolled. Even when research is directed at conditions likely to produce cognitive impairment, individuals with those conditions who are incompetent should not be enrolled if the scientific questions can be answered with subjects who retain the ability to provide informed consent. An exception to this exclusionary rule is when research offers incompetent individuals a prospect of medical benefit at least as favorable as available treatment options in clinical practice. This type of exception is built into the regulations allowing waiver of informed consent in some emergency research.[41,42]

Although no consensus exists on the level of capacity required for informed consent for various types of research, the uncertainty inherent in research and the complexity of decision-making demand that higher thresholds of competence be set for research than treatment decisions. Just as some patients who can make treatment decisions may not be able to give informed consent for research because they are unable to appreciate the differences between clinical practice and clinical research, some patients who are competent to make treatment decisions should be judged incompetent to give informed consent for research

because of the complexities associated with decision making about a particular research protocol. Similarly, individuals who are too impaired to decide for themselves whether to participate in research may still be able to appreciate the meaning of designating someone to make research decisions on their behalf (Fig. 1).

Individuals who lack capacity to give informed consent may be capable of assent—a less demanding standard of research authorization.[43] The US federal regulations on research with children allow them to give assent for research in accordance with their capacities for understanding, appreciation, and reasoning, along with parental permission.[32] Adults who are incapable of giving informed consent may similarly have sufficient ability to assent to research participation. Soliciting assent shows respect for the capacities that they retain as well as for their former autonomy.

Just as incompetent individuals are unable to determine whether to enroll in research, they are similarly unable to decide to withdraw from research. Dissent is widely accepted as sufficient grounds for withdrawing from research. However, it is also generally assumed that valid dissent is a result of a rational decision-making process. It is much harder to know how to respond to behavior suggesting dissent that is not the result of a rational decisional process; for example, dissent that might be voiced by an individual in an acute paranoid psychosis or postconcussive state. Behaviors suggesting objection in these types of cases may represent anxiety, confusion, or ambivalence rather than a rational decision to decline participation. While there is no consensus on what to do when faced with these situations, withdrawing the individual from the research may not always be the most ethically appropriate course of action. Halting the particular procedure and considering reapproach at a different time may also be appropriate. A surrogate decision maker can sometimes be helpful in making these types of determinations. Nevertheless, persistent objection is generally respected by withdrawing the individual from research.[44]

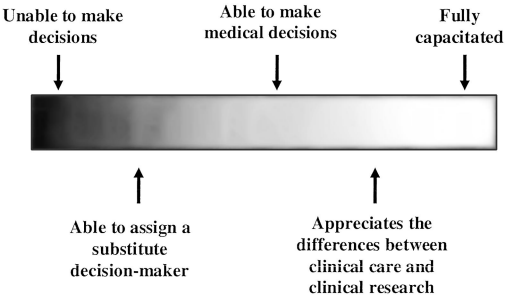


FIG. 1. Decision-making capacity.

## Risk-Benefit Levels Appropriate for Research With Incompetent Adults

While there are no regulations governing risk-benefit assessment for research with incompetent adults, the federal policy framework for research involving children offers valuable guidance. Under this framework, research that provides a prospect of benefit to the child-subject and/or poses minimal risk to subjects is allowed.[32] The regulations define "minimal risk" as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Research that involves a minor increase over minimal risk and does not hold the prospect of benefit for the child-subject may also be justifiable if it fulfills the following conditions: (1) "the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations," (2) "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition," and (3) "adequate provisions are made for soliciting assent of the children and permission of their parents or guardians."[32] Proposed research that has greater than a minor increase over minimal risk and no prospect of benefit for the subjects must be approved by the Secretary of Health and Human Services. These risk-benefit categories seem reasonable to apply to research with incompetent adults, even though there is continued debate over how best to interpret the definitions for the various risk levels.[45,46]

The National Bioethics Advisory Commission (NBAC) recently made policy recommendations

regarding research involving decisionally impaired adults.[1] In their controversial report, they recommended only two levels of risk categorization as opposed to the three levels used in research with children. Reviews of national and international policies, recommendations, and practices reveal disagreement on this matter.[38,47,48]

### Formal Procedures for Capacity Assessment May Be Necessary

As in the case of clinical care, adults are generally presumed competent to consent for research and formal assessments of capacity are not routinely performed. Determinations of competence are ultimately the responsibility of physician-investigators, who are charged with obtaining informed consent. As noted previously, questions about decision-making capacity in clinical situations are frequently referred to a consulting psychiatrist or neurologist with appropriate expertise.

Some commentators have suggested that in research with the potential for enrolling incompetent adults, formal assessment of capacity should be part of the screening process and precede the giving of informed consent for enrollment, regardless of the potential subject's appearance of competence.[26] However, formal capacity assessment of competent adults goes against the presumption of competence afforded to adults and may be an affront to their dignity. Systematic formal assessment of capacity can be incorporated as needed into research on a protocol-by-protocol basis and should be stipulated by IRBs when determined to be important (eg, research on medical conditions with high frequency of cognitive impairment, such as schizophrenia and traumatic brain injury).

Further reflection on the differences between clinical care and clinical research has prompted some commentators to contend that capacity assessment and competence determinations in clinical research should be performed by disinterested third parties.[26] For example, citing concern about potential for conflict of interest among physician-investigators in making judgments about competence, which is not operative for physicians providing personalized clinical care, NBAC adopted a modified version of this approach: "For research protocols that present greater than minimal risk, an IRB should require that an independent, qualified professional assess the potential subject's capacity to consent."[1] In justification of this stance, NBAC asserts, "This requirement of independence is based on NBAC's conviction that conflicts of interest can, in some cases, distort professional judgment, and that they should be eliminated whenever possible."[1]

Nevertheless, the existence of a conflict of interest does not imply that independent capacity assessment is necessarily required.[49] Formal procedures to guide investigators in assessing capacity and determining competence might serve adequately to ensure unbiased judgments. Whenever research is contemplated with subjects at risk of losing decision-making capacity, IRBs should require that investigators describe in the protocol how they plan to assess, and monitor, capacity. Documentation of the capacity assessment should be in the subject's research record, as are documentation supporting other inclusion/exclusion criteria.[50] If independent capacity assessment is required, it generally should be limited to higher-risk studies involving individuals who are likely to have compromised decision-making capacity.

### Surrogate Decision Making Should Take Into Account the Differences Between Clinical Practice and Clinical Research

Except in the case of experimental emergency interventions, enrolling incompetent patients in clinical research can be ethically acceptable only if appropriate surrogate decision makers give informed, prior authorization. While this practice may be ethically acceptable, not all states allow surrogate enrollment of incompetent adults in research.[51] The ethical framework developed for surrogate decision making for treatment decisions offers useful guidance for the research participation of incompetent adults; however, it must take into account the differences between clinical practice and clinical research.

Both standards governing surrogate decisions for treatment, substituted judgment, and best interest have limited applicability to the research context.[52] Everyone is liable to need medical treatment, but most people never need to participate in clinical research. Since research participation may never have been contemplated, individuals at risk of incapacity are less likely to have communicated preferences and values relevant to research participation than to treatment decisions. In some cases, a person's history of research participation may offer guidance. Just as written advance directives

often do not provide helpful guidance for all treatment situations, so they may be even less helpful for research decisions, in view of unanticipated research situations.[53,54] Accordingly, there may be scant evidence to support a substituted judgment for research participation. For research involving adults who have never been competent, no basis exists for a substituted judgment.[55] Additionally, because clinical research is oriented to producing generalizable knowledge for the benefit of individuals in the future, the applicability of a medical best interests standard is questionable or nonexistent for much clinical research. In some cases, however, research participation may offer the prospect of benefits that are greater than what is otherwise available in clinical practice.

The framework developed for enrolling children in research also offers some guidance for use of surrogates in making decisions for incompetent adults, in particular with respect to the issue of assent discussed earlier.[56] Nevertheless, the application of this framework requires reflection on the ways in which parental decision-making differs from surrogate decision-making for incompetent adults. Society grants a wide scope of paternalistic authority for parents in rearing their children. It is not clear that the same scope of discretionary judgment appropriate for parental decisions to enroll their children in clinical research should be accorded to surrogate research decision makers for incompetent adults. Unlike children, incompetent adults may have adult preferences that developed before losing capacity that should guide surrogate decisions. In addition, parental decisions to enroll children in nonbeneficial research, within acceptable limits of risk, may fall within parents' responsibility for educating their children.[57,58] Such research participation may be seen, in part, as a way to teach children about altruism and community service. However, respect for their adult status precludes a parental perspective as a rationale for surrogate authorization of research participation for incompetent adults.

### Assessment and Education of Surrogates

A largely unexplored issue relating to the role of surrogate decision makers in research is the assessment of potential surrogates' ability to perform this role and their dedication to the incompetent adult's well-being. Current policy at the National Institutes of Health's Clinical Center requires an ethics consultation to assist in the selection of surrogates for incompetent adult prospective research subjects.[59] Like patient-volunteers, surrogates may be subject to the therapeutic misconception that confuses clinical research with individualized clinical care. Education for surrogates as well as consultation with a neutral professional or lay advocate may help prepare them for their responsibility to make informed choices on the behalf of incompetent subjects.[52]

### Monitoring the Decision-Making Capacity of Research Subjects

Much more attention has been devoted in the literature to protections at the initial stages of enrollment and obtaining informed consent than to the ongoing monitoring of capacity for research subjects. Nevertheless, some subjects who are capable of giving informed consent at the outset of research participation may lose this capacity at some point during the course of research. These previously capacitated subjects may become sufficiently impaired that they can no longer exercise an informed choice to continue with or withdraw from research participation.

Careful monitoring is important for research in which loss of decision-making capacity is reasonably anticipated. Individuals may lose capacity due to the natural course of their illness. For example, individuals with Alzheimer disease can be expected to have a continued progressive decline in capacity, while individuals with medication-resistant epilepsy can reasonably be expected to have several periods of temporary incapacity during the course of their participation in research. Alternatively, some individuals may be put at risk for losing capacity due to the research procedures. For example, this would apply to individuals with schizophrenia participating in research involving a medication discontinuation phase.[60,61] However, some losses will be unanticipated altogether.

Surrogate decision makers can play a valuable role in subject monitoring and should be consulted by the research team when there are doubts concerning the well being or preferences of incompetent subjects. Surrogates can help determine whether research should go forward or whether the individual should be dropped from the study and provided personalized clinical care. In particular, they may be able to provide guidance as to how to interpret an individual's voicing of dissent at a particular time.

Some researchers have instituted a procedure by which individuals likely to have declining capacity prepare an advance directive at the time of enrollment that includes assigning a surrogate decision maker to take an increasingly active role in decision-making as the subject's own abilities decline.[62] While this model will not work in all protocols, it is a useful way to incorporate surrogate decision makers into a system of safeguards for at-risk subjects.

## Conclusion

### Directions for Future Research

The ethical framework applicable to enrolling incompetent adults in clinical research deserves more systematic exploration and articulation. While the framework for treatment decision making for incompetent adults and the framework for research with children are helpful, they fail in several ethically important ways. More systematic empirical data are needed to better understand the extent to which adults in a variety of conditions have impaired ability to give informed consent to research participation. In addition, too little is known about surrogate decision-making (eg, the motivations of surrogates for enrolling incompetent persons in research, their understanding and appreciation of what research participation involves, their knowledge about the research-relevant preferences and values of the incompetent individuals whose research participation they authorize, and the extent to which they are involved in monitoring research participation). Programmatic experimentation and evaluative research are needed in the areas of enhancing the capabilities of decisionally impaired individuals to give informed consent, formal methods of capacity assessment, independent capacity assessment, consent monitoring, advance directives for research participation, evaluation and education of surrogates, and the use of lay advocates. Funding sources for clinical research involving decisionally impaired individuals should support initiatives to improve the protection of these vulnerable research subjects and to conduct well-designed, ethics-related empirical research.

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## References

1. **National Bioethics Advisory Commission.** Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. Rockville, MD: National Bioethics Advisory Commission; 1998.

2. **Marson DC, Schmitt FA, Ingram KK, et al.** Determining the competency of Alzheimer patients to consent to treatment and research. Alzheimer Dis Assoc Disord 1994;8(Suppl 4):5–18.

3. **Kim SY, Caine ED, Currier GW, et al.** Assessing the competence of persons with Alzheimer's disease in providing informed consent for participation in research. Am J Psychiatry 2001;158:712–717.

4. **Carpenter WT Jr, Gold JM, Lahti AC, et al.** Decisional capacity for informed consent in schizophrenia research. Arch Gen Psychiatry 2000;57:533–538.

5. **Michaud CM, Murray CJ, Bloom BR.** Burden of disease—implications for future research. JAMA 2001;285:535–539.

6. **Smithline HA, Mader TJ, Crenshaw BJ.** Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research? Acad Emerg Med 1999;6:776–780.

7. **Prentice ED, Antonson DL, Leibrock LG, et al.** IRB review of a phase II randomized clinical trial involving incompetent patients suffering from severe closed head injury. IRB 1993;15:1–7.

8. **McAllister TW.** Neuropsychiatric sequelae of head injuries. Psychiatr Clin North Am 1992;15:395–413.

9. **Pereira J, Hanson J, Bruera E.** The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997;79:835–842.

10. **Schifitto G, Kieburtz K, McDermott MP, et al.** Clinical trials in HIV-associated cognitive impairment: cognitive and functional outcomes. Neurology 2001;56:415–418.

11. **Zuccala G, Onder G, Pedone C, et al.** Dose-related impact of alcohol consumption on cognitive function in advanced age: results of a multicenter survey. Alcohol Clin Exp Res 2001;25:1743–1748.

12. **Ambrose ML, Bowden SC, Whelan G.** Working memory impairments in alcohol-dependent participants without clinical amnesia. Alcohol Clin Exp Res 2001;25:185–191.

13. **Slyter H.** Ethical challenges in stroke research. Stroke 1998;29:1725–1729.

14. **Incalzi RA, Chiappini F, Fuso L, et al.** Predicting cognitive decline in patients with hypoxaemic COPD. Respir Med 1998;92:527–533.

15. **Stuss DT, Peterkin I, Guzman DA, et al.** Chronic obstructive pulmonary disease: effects of hypoxia on neurological and neuropsychological measures. J Clin Exp Neuropsychol 1997;19:515–524.

16. **Ellis TE, Berg RA, Franzen MD.** Neuropsychological performance and suicidal behavior in adult psychiatric inpatients. Percept Mot Skills 1992;75:639–647.

17. **Appelbaum PS, Grisso T, Frank E, et al.** Competence of depressed patients for consent to research. Am J Psychiatry 1999;156:1380–1384.

18. **Strachan MWJ, Deary IJ, Ewing FM, et al.** Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. Diabetes Care 1997;20:438–445.

19. **Cosway R, Strachan MW, Dougall A, et al.** Cognitive function and information processing in type 2 diabetes. Diabet Med 2001;18:803–810.

20. **Lemaire F, Blanch L, Cohen SL, et al.** Informed consent for research purposes in intensive care patients in Europe—part I. An official statement of the European Society of Intensive Care Medicine. Working Group on Ethics. Intensive Care Med 1997;23:338–341.

21. **Fost N, Robertson JA.** Deferring consent with incompetent patients in an intensive care unit. IRB 1980;2:5–6.

22. **Jenkins CA, Taube AW, Turner K, et al.** Initial demographic, symptom, and medication profiles in patients admitted to continuing palliative care units. J Pain Symptom Manage 1998;16:163–170.

23. **Casarett DJ, Karlawish JH.** Are special ethical guidelines needed for palliative care research? J Pain Symptom Manage 2000;20:130–139.

24. **Newcomer R, Swan J, Karon S, et al.** Residential care supply and cognitive and physical problem case mix in nursing homes. J Aging Health 2001;13:217–247.

25. **Appelbaum PS.** Patients' competence to consent to neurobiological research. Account Res 1996;4:241–251.

26. **Buchanan AE, Brock DW.** Deciding for Others: The Ethics of Surrogate Decision Making. New York, NY: Cambridge University Press; 1990.

27. **Grisso T, Appelbaum PS.** Assessing Competence to Consent to Treatment. New York, NY: Oxford University Press; 1998.

28. **Appelbaum PS, Grisso T.** Assessing patients' capacities to consent to treatment. N Engl J Med 1988;319:1635–1638.

29. **Drane JF.** The many faces of competency. Hastings Cent Rep 1985;15:17–21.

30. **Beauchamp TL, Childress JF.** Principles of Biomedical Ethics, 4th ed. New York: Oxford University Press; 1994:170–180.

31. **Fried C.** Medical Experimentation: Personal Integrity and Social Policy. Amsterdam: North-Holland Publishing Company; 1974:47–104.

32. **US Department of Health and Human Services.** 45 CFR 46, Protection of Human Subjects, revised November 13, 2001. Washington, DC: US Government Printing Office; 2001. Available at: http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm.

33. **Appelbaum PS, Roth LH.** Competency to consent to research: a psychiatric overview. Arch Gen Psychiatry 1982;39:951–958.

34. **Appelbaum PS, Roth LH, Lidz CW, et al.** False hopes and best data: consent to research and the therapeutic misconception. Hastings Cent Rep 1987;17:20–24.

35. **Joffe S, Cook EF, Cleary PD, et al.** Quality of informed consent in cancer clinical trials: a cross-sectional survey. Lancet 2001;358:1772–1777.

36. **Dunn LB, Lindamer LA, Palmer BW, et al.** Enhancing comprehension of consent for research in older patients with psychosis: a randomized study of a novel consent procedure. Am J Psychiatry 2001;158:1911–1913.

37. **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.** The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: US Government Printing Office; 1979.

38. **Bonnie RJ.** Research with cognitively impaired subjects. Unfinished business in the regulation of human research. Arch Gen Psychiatry 1997;54:105–111.

39. **Wendler D, Prasad K.** Core safeguards for clinical research with adults who are unable to consent. Ann Intern Med 2001;135:514–523.

40. **Wendler D.** Informed consent, exploitation and whether it is possible to conduct human subjects research without either one. Bioethics 2000;14:310–339.

41. **Biros MH, Fish SS, Lewis RJ.** Implementing the Food and Drug Administration's final rule for waiver of informed consent in certain emergency research circumstances. Acad Emerg Med 1999;6:1272–1282.

42. **Adams JG, Wegener J.** Acting without asking: an ethical analysis of the Food and Drug Administration waiver of informed consent for emergency research. Ann Emerg Med 1999;33:218–223.

43. **Leikin S.** Minors' assent, consent, or dissent to medical research. IRB 1993;15:1–7.

44. **Redmon RB.** How children can be respected as 'ends' yet still be used as subjects in non-therapeutic research. J Med Ethics 1986;12:77–82.

45. **Freedman B, Fuks A, Weijer C.** In loco parentis. Minimal risk as an ethical threshold for research upon children. Hastings Cent Rep 1993;23:13–19.

46. **Kopelman LM.** Children as research subjects: a dilemma. J Med Philos 2000;25:745–764.

47. **Cahill M, Wichman A.** Research involving persons with cognitive impairments: results of a survey of Alzheimer disease research centers in the United States. Alzheimer Dis Assoc Disord 2000;14:20–27.

48. **HHS Response to NBAC Report.** Presentation to the National Human Research Protections Advisory Committee on October 31, 2001. Meeting minutes available at: http://ohrp.osophs.dhhs.gov/nhrpac/mtg10–01/mtg1001.html.

49. **Miller FG, Rosenstein DL.** Independent capacity assessment: a critique. Bio Law 1999;11:S432–S439.

50. **Weijer C, Fuks A.** The duty to exclude: excluding people at undue risk from research. Clin Invest Med 1994;17:115–122.

51. **Appelbaum PS.** Involving decisionally impaired subjects in research: the need for legislation. Am J Geriatr Psychiatry. 2002;10:120–124.

52. **Fins JJ, Miller FG.** Enrolling decisionally incapacitated subjects in neuropsychiatric research. CNS Spectrums 2000;5:32–42.

53. **Dresser R.** Planning for future research participation: ethical and practical considerations. Account Res 1999;7:129–136.

54. **Sachs GA.** Advance consent for dementia research. Alzheimer Dis Assoc Disord 1994;8(Suppl 4):19–27.

55. **Weisstub DN, Arboleda-Florez J.** Ethical research with the developmentally disabled. Can J Psychiatry 1997;42:492–496.

56. **Bartholome WG.** Ethical issues in pediatric research. In: Vanderpool HY, ed. The Ethics of Research Involving Human Subjects: Facing the 21st Century. Frederick: University Publishing Group; 1996.

57. **Gaylin W.** The competence of children: no longer all or none. Hastings Cent Rep 1982;12:33–38.

58. **Bartholme W.** Parents, children, and the moral benefits of research. Hastings Cent Rep 1976;6:44–45.

59. **Fletcher JC, Dommel FW Jr, Cowell DD.** Consent to research with impaired human subjects. IRB 1985;7:1–6.

60. **Carpenter WT, Schooler NR, Kane JM.** The rationale and ethics of medication-free research in schizophrenia. Arch Gen Psychiatry 1997;54:401–407.

61. **Rosenstein DL.** IRB review of psychiatric medication discontinuation and symptom-provoking studies. Biol Psychiatry 1999;46:1039–1043.

62. **Dukoff R, Sunderland T.** Durable power of attorney and informed consent with Alzheimer's disease patients: a clinical study. Am J Psychiatry 1997;154:1070–1075.